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APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO.
08/402,394	03/10/95	DORSCHUG	M 02491.0790-0

EXAMINER

HM11/0522

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ART UNIT	PAPER NUMBER
1646	44

DATE MAILED: 05/22/98

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

OFFICE ACTION SUMMARY

☒ Responsive to communication(s) filed on 02 March 1998

☑ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), ~~or thirty days,~~ whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) 21-23, 25-27, 31 is/are pending in the application.
Of the above, claim(s) _____ is/are withdrawn from consideration.
☐ Claim(s) _____ is/are allowed.
☒ Claim(s) 21-23, 25-27, 31 is/are rejected.
☐ Claim(s) _____ is/are objected to.
☐ Claim(s) _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.
☐ The drawing(s) filed on _____ is/are objected to by the Examiner.
☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.
☐ The specification is objected to by the Examiner.
☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.
☐ received in Application No. (Series Code/Serial Number) _____.
☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of Reference Cited, PTO-892
☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____
☐ Interview Summary, PTO-413
☐ Notice of Draftperson's Patent Drawing Review, PTO-948
☐ Notice of Informal Patent Application, PTO-152

--SEE OFFICE ACTION ON THE FOLLOWING PAGES--

★ U.S. GPO: 1996-404-496/40517

The Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1646.

DETAILED ACTION

1. Claims 21 and 22 have been amended and claim 32 has been canceled in the amendment filed 02 March 1998. Claims 21-23, 25-27 and 31 are currently pending and under consideration in the instant application.

2. Any objection or rejection of record which is not expressly repeated in this action has been overcome by Applicant's response and withdrawn.

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Response to Arguments

4. Applicant's arguments filed 02 March 1998 have been fully considered but they are not persuasive.

Claim Rejections - 35 USC § 112

5. Claims 21-23, 25-27 and 31 remain rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to

reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention for the reasons of record.

Applicant argues that "[o]ne skilled in the art would recognize that crystals would only be formed if the pH was the same as the isoelectric point of the fusion protein". This is irrelevant to the issue of new matter in the claims.

Applicant argues that the specification need not describe the claimed invention using the identical words found in the claims in order to satisfy the requirements of 35 U.S.C. 112, first paragraph. This argument was addressed in the previous Office action in which is was stated that "the inherent property of a single embodiment or example in the specification does not provide support for a general idea of a negative limitation" and "the mere absence of a positive limitation does not provide basis for a negative limitation".

Applicant continues to cite MPEP § 2163.07(a) for support of the addition of the negative limitation. This argument was addressed in the previous Office action as well. As stated previously, claiming a "function, theory or advantage" of a device with inherent properties is not the same as including a negative limitation which is present in a single example of the instant application and then claiming that this single embodiment provides basis for the general concept of conditions under which no crystals are formed. Applicant further states that MPEP § 2173.05(I) is not pertinent is not persuasive and still applies to the issue at hand in this rejection and the rejection is maintained.

In summary, Applicant has provided no basis in the instant specification as filed for the negative limitation of "where no crystals are formed"; this is a new inventive concept and not a new wording of the claim as implied by Applicant. Applicant has provided no explanation of how this limitation distinguishes the claimed invention from the prior art (i.e. it does not appear to add any distinguishing feature to the claims). And finally, the limitation of "where no crystals are formed" is neither a "function", "theory" or "advantage", therefore M.P.E.P. § 2163.07(a) would not apply.

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. Claim 21 stands rejected under 35 U.S.C. § 103(a) as being unpatentable over Markussen et al. (U.S. Pat. No. 4,916,212) or Markussen et al. (EPO 163,529) either in view of Goeddel et al. (EPO 055,945), Grau (U.S. Pat. No. 4,801,684) and Grau (U.S. Pat. No. 4,639,332) essentially as applied to the claims in the prior Office actions (paper #'s 32 and 29).

Applicant argues that the references fail (1) to teach or suggest the starting materials used in the claimed process, (2) to teach or suggest the simultaneous addition of trypsin and

carboxypeptidase, (3) to teach a process of producing mono-Arg-insulin under conditions where no crystals are formed (see page 9 of response). With regard to point (1), the starting material of B(1-30)-Arg-A(1-31) is an obvious variant of the preferred embodiment of Markussen et al. and the claimed generic formula of the prior art encompasses Applicant's claimed composition in method step (a). It would have been obvious to one of ordinary skill in the art at the time the invention was made to use this particular embodiment as suggested by Markussen et al. for the production of mono-Arg-insulin as taught by Grau ('332 and '684) because mono-Arg-insulin is exceptionally stable to further tryptic degradation (column 2, lines 10-12 of Grau '332) and makes this species of miniproinsulin an ideal and obvious choice for use in the preparation of mono-Arg-insulin ('212). (See also page 8, beginning line 3 of paper #41 and page 5, beginning line 2 of paper #32 where this argument has been responded to before.) With regard to point (2), the simultaneous addition of trypsin and carboxypeptidase is taught by Grau ('684) see column 5, lines 49-59). With regard to point (3), the limitation of "under conditions where no crystals are formed" is met in that the methods of Markussen demonstrate that the processes take place in an aqueous buffer (acetic acid) with the isolation of the protein via precipitation with acetone (see column 18, lines 42-68 of Markussen '212).

Applicant argues that there is no suggestion to make substitutions to the preferred embodiment of Markussen, nor any reasonable expectation of success. This is not the case because the teachings of Grau ('332 and '684) provide the motivation to produce the starting material which is an obvious variant of Markussen's preferred embodiment. Furthermore,

because B(1-30)-Arg-A(1-31) is encompassed by the generic claim of Markussen, one of ordinary skill in the art would necessarily have a reasonable expectation of success in producing this protein, absent evidence to the contrary.

Applicant argues that the generic formula of Markussen et al. encompasses a very large number of species and that this disclosure does not render obvious the presently claimed starting material of B(1-30)-Arg-A(1-31). However, Markussen alone was not relied upon to render obvious B(1-30)-Arg-A(1-31). As stated above, the additional teaching of Grau ('332 and '684) provide the motivation for selecting this particular embodiment of Markussen et al. in addition to its similarity to the preferred embodiment of Markussen. Therefore, the fact situation of the instant case is different from that presented in *Baird* in that although there may be many species encompassed by the generic claim of Markussen, the preferred embodiment and the teachings of Grau directs the skilled artisan to the species of B(1-30)-Arg-A(1-31) for the reasons of record.

Applicant argues that Grau describes the cleavage of a different compound with the simultaneous addition of trypsin and carboxypeptidase and that there is no reasonable expectation of success that this would work with B(1-30)-Arg-A(1-31) for the production of mono-Arg-insulin. This argument is not persuasive because Grau ('332) specifically identifies mono-Arg-insulin as being an insulin derivative which can be prepared by the recited methods in '332, which includes the simultaneous addition of trypsin and carboxypeptidase (see column 2, lines 49-52).

Applicant argues that the pH range of the reaction in Grau is 7.2 while the instant invention claims a pH of about 6.8. Applicant states "[t]he present invention, however, takes the

novel step of carrying out these reactions at a lower pH, clearly outside the optimal pH range for the enzymes" (see sentence bridging pages 11 and 12 of response). This assertion is not persuasive. It is true that examples which only use trypsin are performed at a pH of 6.8 (see example 4 at page 15, lines 24-27 and example 8 at page 21, lines 13-16). However, when cleavage is performed using trypsin and carboxypeptidase together, the pH is 8.0 (see example 6 at page 17, lines 4-7 and example 10 at page 22). Therefore, Applicant's arguments that the instant invention carries out a "novel step" outside the optimal pH range does not have a basis in fact because the examples provided clearly utilize a pH within the optimum for both trypsin and carboxypeptidase (i.e. pH of 8.0; see examples 6 and 10 of the instant specification). Furthermore, the prior art teaches that when trypsin is added alone, the pH of the reaction is 6.8 (see Grau '332 at column 4, lines 36-40). Because the prior art teaches pH ranges which are exemplified in the instant specification, claims to a pH of 6.8 would be obvious over the prior art of record absent any unexpected advantage of using pH of 6.8. It should be noted that the instant specification provides no examples of a reaction at a pH of 6.8 for the combination of trypsin and carboxypeptidase, therefore, no unexpected results can be relied upon.

Applicant argues that "the Office has not shown that Markussen ('212) can be combined with other references to render obvious the preparation of mono-Arg-insulin or the use of trypsin as a cleavage agent for the generation of mono-Arg-insulin" (see response at page 12). This argument is not persuasive and Applicant is invited to review the rejections of the previous Office

actions. With regard to the use of trypsin as a cleavage agent, this is specifically taught in Grau (see column 4, lines 36-40 of '332).

8. Claim 25 stands rejected under 35 U.S.C. § 103(a) as being unpatentable over Markussen et al. (U.S. Pat. No. 4,916,212) or Markussen et al. (EPO 163,529) either in view of Goeddel et al. (EPO 055,945), Grau (U.S. Pat. No. 4,801,684) and Grau (U.S. Pat. No. 4,639,332), further in view of Mai et al for the reasons of record.

Applicant argues that "claim 25 is not obvious over the prior art as it has a novel and nonobvious bridging member". This argument is not persuasive because Mai et al. that cyanogen bromide cleaves after the amino acid Met and that factor Xa cleaves after the tetrapeptide Ile-Glu-Gly-Arg. (See column 3, line 14, through column 4, line 35, especially column 3, line 67, through column 4, line 1; and column 9, lines 7-19.) Because the primary references of Markussen et al. suggest making fusion proteins that can be cleaved as does Goeddel et al. and Mai et al. teach amino acids which are cleaved by different agents, use of these common cleavage sites would have been prima facie obvious. Applicant has provided no unexpected properties with using these well known cleavage sites. Furthermore, production of fusion proteins was well-known in the art at the time of the instant invention (as demonstrated by Markussen et al. and Goeddel et al.), therefore, there is a reasonable expectation of success and not an "obvious to try" suggestion, absent evidence to the contrary.

9. Claims 22 and 23 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Markussen et al. (U.S. Pat. No. 4,916,212) or Markussen et al. (EPO 163,529) either in view of Goeddel et al. (EPO 055,945), Grau (U.S. Pat. No. 4,801,684) and Grau (U.S. Pat. No. 4,639,332) for the reasons of record.

Applicant argues that the Office has not shown the formation of mono-Arg-insulin as an intermediate (see response at page 14). Applicant should note that the Office is not capable to show the formation of mono-Arg-insulin as an intermediate because laboratory facilities are not available for this purpose. The rejection of paper #41 clearly sets forth the rejection and Applicant has not provided rebuttal. Applicant states that "[n]o evidence has been presented regarding the use of this compound as an intermediate". This is not persuasive because the mere fact that mono-Arg-insulin can be converted to insulin makes it an intermediate for the production of insulin. Because mono-Arg-insulin is stable (as taught by Grau), makes it a preferred intermediate for the production of insulin because this compound could be stored and then converted to insulin at a later time.

10. Claims 26-27 and 31 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Markussen et al. (U.S. Pat. No. 4,916,212) or Markussen et al. (EPO 163,529) either in view of Goeddel et al. (EPO 055,945), Mai et al., Grau (U.S. Pat. No. 4,801,684) and Grau (U.S. Pat. No. 4,639,332), for the reasons of record.

Applicant argues points that have already been addressed and answered above.

Conclusion

11. No claim is allowed.

12. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christine Saoud, Ph.D., whose telephone number is (703) 305-7519. The examiner can normally be reached on Monday to Friday from 8AM to 3PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Stephen Walsh, can be reached on (703) 308-2957. The fax phone number for this Group is (703) 308-0294.

Official papers filed by fax should be directed to (703) 308-4227. Faxed draft or informal communications with the examiner should be directed to (703) 308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Christine Saoud, Ph.D.
May 20, 1998

JOHN ULM
PRIMARY EXAMINER
GROUP 1800